Oxidativ Dem thylation of 4-Substituted *N,N*-Dimethylanilines with Iodine and Calcium Oxide in the Presenc f Methanol

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Reaction of *para*-substituted *N,N*-dimethylarylamines with iodine–calcium oxide in tetrahydrofuran–methanol affords *N*-methylarylamines in good yield.

A direct method for introduction of a C-21 acetoxy group into a 20-ketopregnane is by reaction with iodine–calcium oxide in THF–methanol as described by Ringold and Stork[1] to selectively afford the C-21-iodo-20-ketopregnane with subsequent conversion to the C-21 acetate by treatment with potassium acetate. This procedure is considered to be a relatively simple one and can be carried out in the presence of a variety of other functional groups without adverse results.[2]

When we attempted the iodination of 17β-acetoxy-11β-(4-*N,N*-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione **1** by the Ringold and Stork procedure[1] (Scheme 1), we encountered an unexpected and novel oxidative *N*-demethylation of the *N,N*-dimethylaniline function located at C-11 to afford 17β-acetoxy-11β-(4-*N*-methylaminophenyl)-19-norpregna-4,9-diene-3,20-dione **2**. We could not detect the presence of any C-21 iodinated product in the reaction mixture. Two other steroidal substrates **3** and **5** with the 11β-(4-*N,N*-dimethylaminophenyl) substituent gave similar results and we obtained *N*-demethylated derivatives **4** and **6** in high yield.

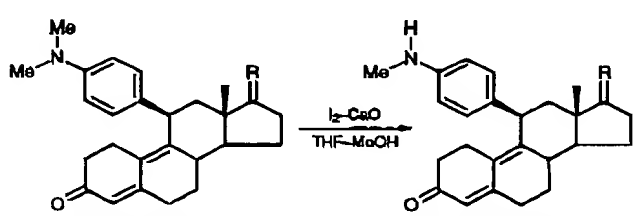
The structures of 11β-(4-*N*-methylaminophenyl) derivatives **2**, **4** and **6** were confirmed through ^{1}H NMR, IR and MS analyses.† The signal of the *N*-methyl protons of **2**, **4** and **6** appears slightly upfield (δ *ca.* 2.80) from the *N,N*-dimethyl signal of **1**, **3** and **5** (δ *ca.* 2.90). On MS analysis, compounds **2**, **4** and **6** all gave correct values for M^+ (*m/z* 461, 419 and 375 respectively) and all share the common fragments of $[MeNH_2Ar]^+$ (*m/z* 107) and $[MeNH_2ArCH]^+$ (*m/z* 120). Further proof was obtained through the independent syntheses of these compounds through copper(I)-catalysed conjugate addition of 4-*N*-methyl-4-*N*-trimethylsilylphenylmagnesiumbromide[3] to an appropriately protected 5α,10α-epoxysteroid.[4]

A typical example for the iodine–calcium oxide *N*-demethylation is as follows. A mixture of **5** (200.0 mg, 0.51 mmol) and calcium oxide (242.0 mg, 4.31 mg, 4.31 mmol) in THF (1.6 ml) and methanol (1.2 ml) was chilled in an ice bath. Iodine (550.0 mg, 1.17 mmol) in THF (0.5 ml) was added. The mixture was stirred at 0 °C for 2.5 h and diluted with methylene chloride. The mixture was filtered and the filtrate was sequentially washed with a 15% sodium thiosulfate solution, water and brine. Evaporation of the solvent and chromatography of the residue on silica gel gave 126.0 mg of **6** (66%).

To the best of our knowledge, oxidative *N*-demethylation with iodine–calcium oxide has never been documented. Ghosal *et al.*[5] have described the oxidation of *N,N*-dimethylaniline with iodine and reported the formation of *N,N,N′,N′*-tetramethylbenzidine and 4-iododimethylaniline. Methods available for oxidative demethylation of amines include metalloporphyrin systems,[6] photooxidative methods,[7] and oxoruthenium(IV) based catalytic systems.[8] These methods share one common feature in that they are all thought to mimic cytochrome P-450 type oxidative behaviour with tertiary amines. However, our attempt to generate **2** for **1** using an oxo(phosphine)ruthenium(IV) complex, according to Takeuchi and coworkers,[8] was not successful.

To further investigate the present oxidative *N*-demethylation, we selected 4-*N,N*-dimethyltoluidine (DMT) **7** as a model compound (Scheme 2). Treatment of DMT with iodine–calcium oxide in THF–methanol gave 4-*N*-methyltoluidine (MMT) **10** in 90% yield, based on HPLC analysis of the crude reaction mixture. The identity of MMT as the major product was confirmed through ^{1}H NMR and GC–MS. Use of DMF instead of THF in the above reaction gave a 1 : 1 mixture of MMT **10** and another material which was characterized (^{1}H NMR and GC–MS) as 4-*N*-methyl-*N*-(methoxymethyl)toluidine **8**. Furthermore, the reaction in DMF–methanol was complete within 15 min., while the reaction in THF–methanol required 3 hours. Under anhydrous conditions, reaction of DMT with iodine–calcium oxide in DMF–methanol afforded **8** as the major product (75%). An authentic sample of **8** was synthesised according to the procedure of Murahashi[9] *et al.* for direct comparison with the product obtained by the reaction with iodine–calcium oxide. We established their identity by comparison of ^{1}H NMR spectra and identical R_t on HPLC analysis of the crude reaction mixture. Efforts to purify **8** were unsuccessful, for the material was readily transformed to generate MMT **10**. Furthermore, treatment of **8** with aqueous HCl afforded **10** in excellent yield. We later confirmed the presence of **8** in small amounts (*ca.* 5–10%) in the reactions using THF–methanol.

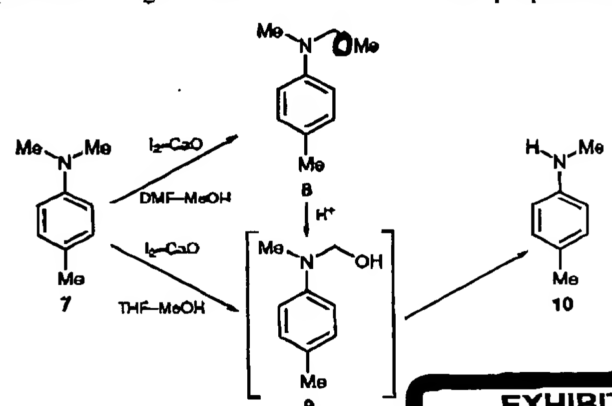
We believe the present oxidative *N*-demethylation to proceed through a mechanism similar to those proposed for



1 R = β-COMe, α-OAc
3 R = β-COMe, α-OH
5 R = O

2 R = β-COMe, α-OAc
4 R = β-COMe, α-OH
6 R = O

Scheme 1



Scheme 2

cytochrome P-450 type oxidative dealkylation of amines.[6-9] These mechanisms propose the formation of an iminium cation, generated either by two one-electron transfers *via* a radical cation intermediate or a two-electron transfer followed by loss of a proton. Apparently, in the present case, the initial step is the formation of an iodine–amine charge-transfer complex[5] which subsequently collapses to the iminium cation. Nucleophilic attack on the iminium cation by methanol yields the methoxymethyl amine **8** which on hydrolysis results in the monomethyl amine **10**.

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Footnote

† Satisfactory elemental analyses were obtained for all new compounds.

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